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Tau immunotherapies: Lessons learned, current status and future considerations

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Abstract

The majority of clinical trials targeting the tau protein in Alzheimer's disease and other tauopathies are tau immunotherapies. Because tau pathology correlates better with the degree of dementia than amyloid- β lesions, targeting tau is likely to be more effective in improving cognition than clearing amyloid- β in Alzheimer's disease. However, the development of tau therapies is in many ways more complex than for amyloid- β therapies as briefly outlined in this review. Most of the trials are on humanized antibodies, which may have very different properties than the original mouse antibodies. The impact of these differences are to a large extent unknown, can be difficult to decipher, and may not always be properly considered. Furthermore, the ideal antibody properties for efficacy are not well established and can depend on several factors. However, considering the varied approaches in clinical trials, there is a general optimism that at least some of these trials may provide functional benefits to patients suffering of various tauopathies.

1. Introduction

Currently there are nine different tau antibodies and two tau vaccines in clinical trials and several more in late-stage preclinical development, which represents an exciting time in the field of tau immunotherapy. However, relatively speaking, tau immunotherapy is still in the early days of development. One main challenge in the study of tau pathology is the immense diversity of the pool of physiological and pathological tau molecules (Colin et al., 2020; Holth et al., 2019b; Novak et al., 2018). Alternative splicing gives rise to six tau isoforms in the CNS (Spillantini and Goedert, 2013), and the picture is further complicated by the more than 80 possible phosphorylation sites and the interplay of kinases and phosphatase that alter tau's phosphorylation pattern (Grundke-Iqbal et al., 1986; Iqbal et al., 2016). A myriad of post-translational modifications, such as hyperphosphorylation, glycosylation, ubiquitination, glycation, polyamination, amidation, nitration, sumoylation, oxidation,

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proteolysis, and aggregation add to the complexity of therapeutically targeting this protein (Bittar et al., 2020; Congdon and Sigurdsson, 2018; Gong et al., 2005; Jadhav et al., 2019; Martin et al., 2011). As a result, these modifications create a pool of diverse tau molecules, often referred to as the tau proteome and different tau proteomes, that exist in health and disease states (Novak et al., 2018). While the “Alzheimer’s disease (AD) tau proteome” denotes the entire range of tau forms and derivatives present in AD, there are both similarities and differences in the proteomes across tauopathies, challenging the search for an effective therapeutic. A majority of tau immunotherapy clinical trials are enrolling patients with AD or have advanced to include such patients. However, more recently trials have been initiated on patients with primary tauopathies, mostly on the most common one, progressive supranuclear palsy (PSP), but lately on rarer tauopathies.

While major advancements have been made, and while we continue to learn from what are deemed “failures” in the field and related fields, there are key considerations that should be made in the continued search for an effective disease modifying therapeutic, as it relates to tau immunotherapies. These include but are not limited to 1) the characteristics of the tau antibody (i.e. isotype, epitope, charge, affinity, and size); 2) the type of tauopathy being targeted; 3) the pathological progression of the tauopathy; and 4) prevention of tau toxicity versus tau seeding.

The purpose of this review is to highlight various uncertainties and barriers to success and discuss how future research and clinical trials might address past limitations. Additionally, we provide an up-to-date status of current clinical trials already underway.

2. Antibody-mediated tau clearance mechanisms

The majority of anti-tau immunotherapy approaches involve whole antibodies and one of the clinical candidates is an autoantibody derived from a human. Published findings from us and others show that tau antibodies can act extracellularly and intracellularly (Asuni et al., 2007; Bright et al., 2015; Castillo-Carranza et al., 2014b; Collin et al., 2014; Congdon et al., 2019a; Congdon et al., 2013; Congdon et al., 2016; d’Abramo et al., 2015; Gu et al., 2013; Kondo et al., 2015; Krishnamurthy et al., 2011; Krishnaswamy et al., 2014; McEwan et al., 2017; Shamir et al., 2016; Wu et al., 2018; Yanamandra et al., 2015). Pathological tau mostly resides within neurons, but in certain individuals and/or tauopathies, it is also evident in glia (Leyns and Holtzman, 2017). A much smaller pool of tau is found extracellularly in the form of monomers and oligomers/small aggregates, or as remnants of neurofibrillary tangles following the death of the neuron. These may all contribute to the spreading of tau pathology (Hanger et al., 2014; Sebastian-Serrano et al., 2018; Yamada, 2017) (more on this below, in the Type of Tauopathy: Intracellular vs Extracellular Target section).

Some anti-tau antibodies are not readily taken up into neurons, presumably because of their unfavorable charge (Congdon et al., 2019a) (more on this below in Characteristics of the Tau Antibody – Epitope, isotype, charge, affinity, and size); therefore, they work principally in the extracellular compartment. Within this compartment, antibodies might sequester tau aggregates, interfere with their assembly and promote microglial phagocytosis, with the overall effect of blocking the spread of tau pathology between neurons. Other antibodies are

easily detected within neurons, entering primarily via receptor-mediated uptake (Congdon et al., 2013; Gu et al., 2013), and have been shown to work both intracellularly and extracellularly (Congdon et al., 2019a; Congdon et al., 2016; Wu et al., 2018). Once internalized, these antibodies bind to tau aggregates within the endosomal–lysosomal system and are likely to promote their disassembly. This would then lead to enhanced access of lysosomal enzymes to degrade the aggregates. Further, these antibodies could act to sequester tau assemblies in the cytosol and to prevent their release from the neuron, or to promote proteasomal degradation via E3 ubiquitin–protein ligase TRIM21 binding (McEwan et al., 2017). While many questions still remain regarding the specifics of antibody-mediated tau clearance, the most clinically efficacious antibodies are likely to target more than one pathway and/or pool of tau (Congdon and Sigurdsson, 2018).

3. Characteristics of the tau antibody – Isotype, epitope, charge, affinity, and size

It is now evident, based on the significant increase in available literature, that various features of a tau antibody can greatly impact its mechanism of action and overall efficacy. The impact of some of these features, such as epitope, are not surprising given what we have learned from studies and trials targeting A β and other proteinopathy aggregates. Others, such as isotype, charge, affinity, and size, are more nuanced and have been less explored. Further, many of these features are interrelated, making teasing apart their individual impacts challenging.

Isotype:

Macrophages and microglia have been implicated as effector cells in the central nervous system (CNS) following immunotherapy; however, recent data suggests a broader expression pattern of Fc receptors (FcRs) in the human CNS (Fuller et al., 2014). The Fc part of immunoglobulins G (IgGs) binds to specific Fc gamma receptors (Fc γ R), which are expressed in neurons, microglia, and astrocytes. All of the Fc γ R belong to the immunoglobulin superfamily, which differ in their antibody affinities due to their different molecular structure (Indik et al., 1995). While initially debated, a number of studies now show the presence of neuronal Fc γ Rs (Andoh and Kuraishi, 2004; Fernandez-Vizarra et al., 2012; Suemitsu et al., 2010; van der Kleij et al., 2010), and support the uptake of antibodies into neurons for acute tau protein clearance (Asuni et al., 2007; Collin et al., 2014; Congdon et al., 2019a; Congdon et al., 2013; Congdon et al., 2016; Gu et al., 2013; Kondo et al., 2015; Krishnamurthy et al., 2011; Krishnaswamy et al., 2014; McEwan et al., 2017; Shamir et al., 2016; Wu et al., 2018).

There are four different isotypes of human IgG (IgG1, IgG2, IgG3, and IgG4), which have varying affinities for the Fc γ R. IgG1 is most effective in promoting microglia and macrophage phagocytosis, whereas IgG4 is least effective to facilitate that clearance pathway (Bruhns and Jonsson, 2015). In this context, it is interesting that most of the tau antibodies in clinical trials are effectorless (IgG4 or mutated effectorless IgG1 – isotypes have not been revealed for all), although many are described to only work extracellularly. This would appear to reduce their efficacy as phagocytosis could not be recruited to degrade

the tau-antibody complex. Other potential limitations of targeting extracellular tau are further discussed in the Type of Tauopathy: Intracellular vs Extracellular Target and Prevention of Toxicity vs Seeding sections below.

Further, the notion of whether or not an antibody should possess an effector function, to facilitate microglial phagocytosis of the antibody-tau complex, in order to be efficacious remains relatively unexplored. One such direct comparison suggests that an effector function is not necessary in clearing pathological tau (Lee et al., 2016), but the otherwise identical antibodies, with or without effector function, were not always compared in the study. Another study showed that tau antibodies enhance microglial clearance of pathological tau in an Fc-dependent manner, with the whole antibody being more effective than its Fab fragment (Luo et al., 2015). Similar conflicting results were previously reported for A β targeting antibodies (Bacskai et al., 2002; Bard et al., 2003; Das et al., 2003). Furthermore, a previous report compared two antibodies with a similar binding epitope (phosphorylated serine 404) and comparable affinity found that effector function is necessary (Ittner et al., 2015). It should be kept in mind that mouse antibody isotype terminology differs from the human terminology. Most mouse studies on tau antibody therapies have been conducted with IgG1 antibodies because it is the most abundant mouse isotype coming out of hybridoma screening. Mouse IgG1 is not thought to stimulate phagocytosis to the same degree as human IgG1. Conversely, a few studies in this field have been conducted with mouse IgG3 antibodies, which is comparably neutral with regard to phagocytosis as human IgG4. Antibody isotype may also influence intracellular-targeting receptor-mediated uptake, which relies on the Fc portion (Congdon et al., 2013; Kondo et al., 2015). Clearly, more work is needed to better elucidate the importance of this antibody feature for efficacy.

Epitope:

In regard to epitope, we initially and now many others have shown the serine 396/404 epitope as being an efficacious therapeutic target (Asuni et al., 2007; Bi et al., 2011; Boutajangout et al., 2011; Boutajangout et al., 2010; Chai et al., 2011; Congdon et al., 2013; Congdon et al., 2016; Gu et al., 2013; Ittner et al., 2015; Krishnamurthy et al., 2011; Liu et al., 2016; Nobuhara et al., 2017; Rajamohamedsait et al., 2017; Rosenqvist et al., 2018; Sankaranarayanan et al., 2015; Theunis et al., 2013; Umeda et al., 2015; Wu et al., 2018) and the crystal structures of some of these antibodies have been reported (Chukwu et al., 2019; Chukwu et al., 2018). These findings have translated to clinical trials, with the active vaccine ACI-35, which targets this epitope (ISRCTN.com, 2013; Theunis et al., 2013) and most recently with an antibody Lu AF87908 (ClinicalTrials.gov, 2019e; Rosenqvist et al., 2018). Additional epitopes have been targeted and shown promise. These include epitopes that are non-phosphorylated (Agadjanyan et al., 2017; Dai et al., 2015; Dai et al., 2017; Davtyan et al., 2017; Funk et al., 2015; Kfoury et al., 2012; Nobuhara et al., 2017; Yanamandra et al., 2015; Yanamandra et al., 2013; Yanamandra et al., 2017), phosphorylated (Collin et al., 2014; d'Abramo et al., 2015; Nobuhara et al., 2017; Sankaranarayanan et al., 2015; Subramanian et al., 2017; Troquier et al., 2012; Umeda et al., 2015; Walls et al., 2014), conformational/oligomeric (Castillo-Carranza et al., 2014a; Castillo-Carranza et al., 2014b; Chai et al., 2011; d'Abramo et al., 2013; Kondo et al., 2015; Luo et al., 2015; Schroeder et al., 2016), and truncated (Modak and Sigurdsson, 2017; Modak et al., 2015;

Nobuhara et al., 2017). Furthermore, recent research highlights that some tau epitopes may not be accessible on the majority of tau seeds and that high-affinity tau antibodies show dramatic differences in their ability to block tau seeding in vitro (Albert et al., 2019; Courade et al., 2018) (this topic is discussed further in Prevention of Toxicity vs Seeding below). Of course directly comparing studies is challenging, based on a mix of differences in design, affinity, isotype, and charge; however, it is likely that each may be beneficial in their own way, possibly as it relates to the type of tauopathy being targeted and the pathological progression of the disease state.

Charge:

Antibody charge has emerged as not only an important feature, but also a multifaceted one. This feature likely explains why some reports have detected tau antibodies inside neurons (Asuni et al., 2007; Collin et al., 2014; Congdon et al., 2019a; Congdon et al., 2013; Congdon et al., 2016; Gu et al., 2013; Kondo et al., 2015; Krishnamurthy et al., 2011; Krishnaswamy et al., 2014; McEwan et al., 2017; Shamir et al., 2016; Wu et al., 2018), whereas others do not for different antibodies (Bright et al., 2015; Castillo-Carranza et al., 2014b; d'Abramo et al., 2015; Yanamandra et al., 2015). Examining this issue, we showed that tau antibodies against different tau epitopes (1B9: P-Thr212/P-Ser 214; 2C11: P-Ser262; Tau-5: 210–244; and 4E6: P-Ser396/404) are taken up to varying degree in primary neuronal cultures from tauopathy mice (Congdon et al., 2019a). The extent to which uptake is achieved and subsequent efficacy may be explained, in part, by their respective charges, as defined by their isoelectric point (IEP). More specifically, compared to the 4E6 antibody (IEP = 6.5), the other antibodies showed significantly less uptake (1B9 IEP = 8.0; 2C11 IEP = 7.8; Tau-5 IEP = 5.1), suggesting an ideal IEP being slightly acidic, as compared to more acidic or basic antibodies. However, because each one of these antibodies targets a different epitope, and therefore cannot be directly compared, we partially humanized the 4E6 antibody (h4E6), in which the Fc region and part of the non-binding Fab region were replaced with a human scaffold. This resulted in a robust shift in charge, from an IEP of 6.5–9.6, and significantly altered its binding characteristics, neuronal uptake, and ability to prevent tau toxicity. However, under certain conditions, it did prevent pathological seeding of tau. These data highlight the need for thorough antibody characterization, namely following chimerization/humanization of mouse monoclonal antibodies, prior to clinical trials. This may require further engineering to maintain or improve therapeutic potential, as the ideal clinical candidate may be very different from its mouse counterpart even though the antibody sequences that directly participate in binding (complementary determining regions (CDRs) are the same, as was the case in our study.

Affinity:

While seemingly straightforward, the influence of antibody affinity is not as clear-cut as once believed. We have previously reported that a low affinity antibody against the phosphorylated serine 396/404 region is effective in various culture and in vivo models (Congdon et al., 2019a; Congdon et al., 2013; Gu et al., 2013; Wu et al., 2018), while a high affinity antibody against the same region is ineffective in the same models but more promising as a diagnostic imaging probe (Congdon et al., 2016; Krishnaswamy et al., 2014; Wu et al., 2018). Importantly, the antibodies are of the same mouse isotype (IgG1 κ) but

differ in their binding profile against various tau peptides and tau species from mice and humans. Further, our preliminary data has shown better efficacy in various models of a high affinity antibody against tau truncated at aspartate 421 vs. a low affinity antibody against that epitope (Modak and Sigurdsson, 2017; Modak et al., 2015). Similarly, it has been demonstrated by others that a low affinity antibody against a conformational epitope (MC1; aa7–9 and 312–342 (Jicha et al., 1997)) is effective in a mouse model of tauopathy, whereas a high affinity antibody, DA31, recognizing total tau (aa150–190) was ineffective (d'Abramo et al., 2013). Certainly, the difference in epitopes may be a mediating factor, making teasing apart the impact of affinity difficult; however, these data lend to the notion that antibody affinity does not equal efficacy. Others have also postulated that selectivity and epitope is more important than affinity (Albert et al., 2019; Courade et al., 2018; Jadhav et al., 2019). Furthermore, we have shown that partial humanization of a consistently effective mouse tau antibody, 4E6, enhanced its affinity for various aggregated and insoluble tau species yet rendered it ineffective or less effective in tauopathy culture models (Congdon et al., 2019a). This high affinity for various tau forms that may be relatively inert likely neutralized the antibody so that it was not available to bind to more toxic soluble forms of tau. Additionally, its charge was very different from its mouse counterpart, which limited its neuronal uptake, and thereby efficacy as well. Others have used directed evolution to increase affinity and generate a singlechain variable fragment (scFv) of a high-specificity antibody (Li et al., 2018), but stressed the importance of assessing the specificity as part of the engineering process, as significant increases in non-specific binding can occur, suggesting a tradeoff between affinity and specificity, in some of the generated clones.

Size:

All of the antibodies in clinical trial are whole antibodies (150 kDa); however, much less attention has been paid to smaller antibody fragments such as scFvs (25 kDa) and single domain antibody fragments (sdAbs; 13 kDa) also referred to as variable domain of the heavy chain only antibody (VHHs), which have certain advantages that justify further exploration of their therapeutic and diagnostic potential (Belanger et al., 2019; David et al., 2014; Harmsen and De Haard, 2007; Messer and Butler, 2020; Pain et al., 2015). Importantly, their small size allows for better tissue penetration than whole antibodies (Pizzo et al., 2018). This is particularly important when the target is primarily within the brain and inside neurons, such as tau, thus providing even greater therapeutic promise. As mentioned above, effectorless anti-tau antibodies have been shown to be sufficient to protect neurons from toxic tau (Lee et al., 2016), supporting the therapeutic potential of antibody fragments lacking a Fc region, such as sdAbs (VHHs) (see though further discussion in the Characteristics of the Tau Antibody section).

When tau antibody fragments have been examined, they have often been scFvs, but those were not compared to otherwise comparable whole antibodies with the same CDR regions, and used ultrasound, a carrier protein or vectored expression (Ising et al., 2017; Nisbet et al., 2017; Spencer et al., 2018; Vitale et al., 2018), which makes examining the impact of size alone more difficult. We have compared whole antibodies, 4E6 and 6B2 against the phosphorylated serine 396/404 region to their single Fab fragments (50 kDa) and found increased uptake of Fab fragments in both tauopathy and wild-type brain slices, relative to

whole antibodies (Gu et al., 2013). These findings were quite interesting as Fab fragments are taken up by bulk-mediated endocytosis, which is a much less prominent uptake pathway for whole antibodies, with 20% being bulk-mediated and 80% being receptor-mediated (Congdon et al., 2013). Bulk-mediated endocytosis is also less specific than receptor-mediated endocytosis, so while more of the fragments may enter the brain and neurons because of their smaller size, it is also possible that more of them could be lost via non-specific uptake and subsequent degradation or secretion. We have also shown that whole tau antibodies are cleared much faster in wild-type neurons than in tauopathy neurons, as detected by multi-photon imaging (Wu et al., 2018). This is presumably because the wild-type neurons lack tau aggregates for the antibodies to bind to. Furthermore, antibody fragments have much shorter half-life (minutes to hours) than whole antibodies, (1–3 weeks); therefore, they need to be modified prior to in vivo therapeutic administration. Alternatively, they could be delivered as gene therapies (Messer and Butler, 2020). sdAbs in particular are more suitable as such than whole antibodies because their single unit and small size increases the likelihood of proper folding within the cell to maintain efficacy. A direct comparison in efficacy between whole antibodies and their scFv or sdAb fragments has yet to be reported but we recently showed robust efficacy of an scFv in a fly model (Krishnaswamy et al., 2020), whereas the parent antibody, 6B2, is ineffective in various in vivo and culture models as discussed above (Congdon et al., 2016; Wu et al., 2018). While the reason for this discrepancy may be multifaceted and model dependent, a possible explanation may be that the scFv has a lower affinity for tau than 6B2 (Krishnaswamy et al., 2014). Binding of a high affinity antibody to tau aggregates in the lysosomes may render these aggregates more compact than therefore resistant to enzymatic degradation, whereas low affinity antibody may interfere with tau aggregate assembly and thereby facilitate their enzymatic degradation within the lysosomes. We and others are currently investigating the utilization of even smaller fragments that contain only a heavy chain variable region for efficacy and diagnostic imaging potential in tauopathies and other proteinopathies (Congdon et al., 2019b; Dupre et al., 2019; Li et al., 2016; Marchal et al., 2019; Sandusky-Beltran et al., 2019). Importantly, little is known regarding the impact of charge on antibody fragment uptake; however, VHH transmigration has been shown to be charge dependent (Li et al., 2012).

4. Type of tauopathy: Intracellular vs extracellular target

While it is easy to appreciate the differences between and within the different tauopathies, there are specific considerations that should be made as it relates to tau immunotherapy. These include the respective presence and abundance of intracellular and extracellular pools of tau and the epitopes that are observed and/or exposed across tauopathies, that impact whether a potential antibody is clinically a ‘good fit’ based on these features.

Tau is primarily an intracellular protein, both in its normal physiological form and in its pathological form as aggregates of various sizes that can form neurofibrillary tangles. Tau protein can also be released from neurons and is found in the interstitial fluid (ISF) (Bright et al., 2015; Chai et al., 2012; Holth et al., 2019a; Takeda et al., 2015; Yamada et al., 2011; Yamada et al., 2014) and cerebrospinal fluid (CSF) (Cicognola et al., 2019; Holth et al., 2019b; Meredith et al., 2013; Sato et al., 2018; Sengupta et al., 2017), which is thought to

contribute to the spreading of neuropathology and disease progression (Tsai and Boxer, 2016; Walker et al., 2013). However, the levels of tau in ISF and CSF in experimental animals (Yamada et al., 2011) and in CSF in humans (Holth et al., 2019b; Sato et al., 2018) is comparatively low to that of intracellular tau. To put this into perspective, a recent study assessed these two pools of tau (intracellular and extracellular) in a group of AD patients and subjects with mild cognitive impairment (MCI), compared to age-matched controls (Han et al., 2017). In this study it was estimated that CSF tau is roughly 0.001–0.0001% of total brain soluble tau; however, it is conceivable that by the time tau reaches the CSF it has been largely degraded. In one transgenic tauopathy mouse model (P301S) it was found that ISF tau decreases with age, which was attributed to progressive increases in intracellular tau aggregation formation and accumulation. Interestingly, while absolute values indicated that CSF tau is approximately 10% of tau levels in ISF in these mice, the amount of tau in these two pools did not correlate in individual animals, suggesting independent regulation (Yamada et al., 2011). Levels of ISF tau have also been quantified in human traumatic brain injury (TBI) patients, where pericontusional regions display elevations in ISF tau compared to normal-appearing tissue (Magnoni et al., 2012) and ISF tau levels correlate with diffusion tensor imaging (DTI)-based measurements of white-matter integrity (Magnoni et al., 2015); however, in both studies intracellular tau levels could not be obtained for relative comparison. Applying the aforementioned ratios in humans, it can be estimated that the extracellular tau available to be targeted is about 0.01–0.001% of intracellular tau. Tau antibodies have been shown to target tau intracellularly and extracellularly and thus hold great therapeutic promise across various neuropathological conditions where aberrant tau is present; however, the majority of tau and the most likely to be clinically beneficial target is that of intracellular tau (Congdon and Sigurdsson, 2018; Sigurdsson, 2018, 2019).

In further regard to presence and abundance of intracellular and extracellular pools of tau, it has become increasingly clear that ratios of these pools vary across tauopathies, based in large part on the profiling of the CSF. For example, it has been shown that tau is increased in the CSF of AD patients, but not in various other tauopathy patients, compared to controls (Barthelemy et al., 2016; Coughlin and Irwin, 2017; Hales and Hu, 2013; Olsson et al., 2016). This suggests that extracellular pools may be significantly lower in non-AD tauopathies and thus an antibody that only targets extracellular tau may be less efficacious in this specific patient population, an argument that has been made by us previously and others (Colin et al., 2020; Sigurdsson, 2017, 2018).

With this in mind, it was recently announced that AbbVie had called a halt to the Phase 2 trial of the N-terminally and extracellularly targeting C2N-8E12 in patients with PSP due to a failed futility analysis. While limited information has been made public, because PSP patients do not present with increased CSF tau, targeting extracellular tau in this specific patient population may not affect disease progression or alleviate its symptoms. This antibody continues to be assessed in AD patients. Another antibody that also targets N-terminal extracellular tau, Biogen's BIIB092 was deemed safe and well-tolerated in PSP patients, and showed suppression of N-terminal tau in CSF by 90 percent (Boxer et al., 2019); however, it was recently announced that it showed no efficacy, as measured by change on the PSP rating scale, in a Phase 2 trial in PSP patients. As such, Biogen has ended the development of the antibody for PSP and other primary tauopathies, but is continuing

trials in people with MCI due to AD ([Alzforum.org](https://www.alzforum.org), 2019b; [Investors.biogen.com](https://investors.biogen.com), 2019). Results from continued trials will be particularly insightful as to whether immunotherapy targeting extracellular tau may be better suited for AD than PSP.

Furthermore, and in regard to exposed/available epitopes within extracellular pools, mass spectroscopy studies show that most of CSF tau is comprised of fragments that lack N- and C-termini and approximately consist of Tau150–250 (Barthelemy et al., 2016; Sato et al., 2018). As previously mentioned, tau may be significantly degraded by the time it reaches the CSF, but this suggests that an extracellularly acting antibody directed against a mid-domain region of tau (Tau150–250) might be more efficacious than ones directed against either N- or C-termini (Albert et al., 2019; Courade et al., 2018). Alternatively, an antibody that is taken up intracellularly will likely have access to additional exposed/available epitopes beyond the mid-domain region found in CSF and is likely to be more efficacious. Recent developments in tau immunotherapy clinical trials support these points, as outlined in below.

However, it would be remiss not to address the notion that toxic species in the extracellular space, be it CSF or ISF, are still not well defined especially in comparison to the more abundant intracellular tau species. This limitation is likely in large part due to the relatively low levels of tau that exist in the extracellular space, which make threshold of detection difficult. Furthermore, access to CSF and/or ISF is limited by resources, as these sample types can be very costly to obtain by basic researchers. As sensitivity increases for methods of detection, a deeper understanding of all the species that exist in the extracellular space, be it in human or mice, will surely follow.

5. Pathological progression of the tauopathy

If there is one thing we have learned from past clinical trials, targeting either amyloid-beta (A β) or tau, it's that enrollment of participants earlier in the pathological progression of the tauopathy is likely a key determinant of efficacy. However, accurate diagnosis prior to enrollment is reliant upon sensitivity of imaging agents and/or quantification of tau in the CSF and/or blood.

It is a well-known phenomenon that the pathological progression of tauopathies is accompanied by the presence of certain tau epitopes, and as such certain antibodies may work better or worse based on the stage of the given tauopathy. Furthermore, antibody-derived ligands offer increased target specificity as a major advantage over traditional small molecule imaging agents, and could provide insight into the relative abundance of different tau epitopes (Krishnaswamy et al., 2014).

6. Prevention of toxicity vs seeding

It is now well-established that various peptide/protein aggregates can be seeded in vitro and in vivo, and that these seeds can spread through anatomically connected pathways (Goedert et al., 2010; Goedert et al., 2014; Guo and Lee, 2011; Mudher et al., 2017; Sigurdsson et al., 2002; Walker et al., 2013). It has also been established that different molecular conformers (or strains) of aggregated tau exist, based on the fact that several human tauopathies have distinct fibril morphologies (Arakhamia et al., 2020; Falcon et al., 2018; Fitzpatrick et al.,

2017; Gerson et al., 2014; Goedert and Spillantini, 2017), and possess unique seed-competencies (Dujardin et al., 2018; Gerson and Kaye, 2013; Kaufman et al., 2016). Namely, extracellular tau has been implicated in the transneuronal propagation of tau pathology in cell-based and mouse models, and has been proposed to explain the stereotypical progression of tau pathology in Alzheimer's disease (Braak and Del Tredici, 2011; Clavaguera et al., 2009). As such, the incorporation of this phenomenon into antibody efficacy studies, through the use of human AD-derived or transgenic mouse brain homogenates in vitro and in vivo, has been popular and, in many ways, appropriate (Albert et al., 2019; Dai et al., 2018; Rosenqvist et al., 2018; Yanamandra et al., 2013). However, it is also important to note that tau seeding or spreading may not necessarily be directly linked to more acute tau toxicity, as defined by loss of neurons/neuronal processes or deterioration of their function. Both features are likely important for disease manifestation, and enough seeding will eventually produce toxicity, but may need to be tackled by different sets of antibodies, each of which may be more efficacious in certain tauopathies or at different stages of disease progression.

We have observed that preventing tau seeding and blocking tau toxicity, or neuronal loss, are not necessarily intrinsically linked. Specifically, we have shown that an antibody against the P-[Thr212, Ser214] tau region prevented tau seeding but not tau toxicity, which was measured by quantifying NeuN as a neuronal marker (Congdon et al., 2019a), which in this case was linked more to loss of neuronal processes than overt neuronal death. These findings can be explained by the tau species to which it binds, which may promote seeding without toxicity. Another explanation for the disconnect, at least in culture, is that the toxicity pathway appears to be more acute whereas the seeding pathway is more gradual. It is possible in vivo that certain forms of tau assemblies may be acutely toxic, whereas other forms may be more prone to seeding. Eventually seeding would presumably have deleterious effects, but this may also be an endogenous effort by the cell to sequester toxic forms of tau. With that, prevention of seeding by an antibody may unleash some forms that are less toxic when sequestered in aggregates. This notion is supported by work from the prion field, showing that prion replication can be separated from toxicity and that some forms of prion aggregates may actually delay the onset of clinical symptoms (Diaz-Espinoza et al., 2018; Sandberg et al., 2011). As we have done, using antibodies as tools to neutralize certain tau species provides an insight into this matter, showing some overlap between seeding and toxicity, but also that these can exist as separate entities.

Furthermore, how antibodies can affect the different pathways of acute toxicity and chronic spreading is likely epitope-dependent, and can be even further explained by binding differences within the same region (Congdon et al., 2016). To best determine which antibodies are sufficient to advance to clinical trial, it is important to include various assays that can distinguish and assess both toxicity and seeding. Ideally, a clinical candidate antibody would perform well in both types of assays, assuming that preventing the latter does not exacerbate the former, but it appears that much more attention is being paid to interfering with tau seeding/aggregation/propagation and that prevention of toxicity is typically a secondary measure, if assessed at all. Importantly, an antibody that impacts the neurotoxicity pathway may be more relevant for identifying therapies that could quickly

provide cognitive improvements, as compared to the functional benefits of targeting the more chronic seeding pathway, which may take longer to manifest.

7. Brief summary of past clinical trials and Current Updates from Ongoing Clinical Trials

While we have previously reviewed past and current tau clinical trials elsewhere (Congdon and Sigurdsson, 2018; Pedersen and Sigurdsson, 2015; Sigurdsson, 2016, 2018), we would like this section to provide an update on the recent developments since past publications as well as a brief review of past or discontinued trials. Please refer to Table 1 for all tau immunotherapy clinical trials.

AADvac-1:

Developed by Axon Neuroscience SE and inspired by research on tau cleavage generating N-terminally truncated fragments (Paholikova et al., 2015), this is an active vaccine that uses a synthetic tau peptide derived from amino acids 294–305 of the tau sequence (KDNIKHVPGGGS) that is linked to keyhole limpet hemocyanin and was initially administered in aluminum hydroxide adjuvant to AD patients (Kontsekova et al., 2014; Novak et al., 2017).

The Phase 1 clinical trial used three subcutaneous monthly injections of a single dose of AADvac-1, and safety, tolerability, and immunogenicity were assessed, along with an exploratory assessment of cognition (Novak et al., 2017). After this, patients then entered the open-label phase, and another three doses at monthly intervals were administered. After that, patients could enroll in a follow-up study lasting a further 18-months. The primary endpoint was all-cause treatment-emergent adverse events, with a separate analysis for injection site reactions and other adverse events. Five patients had serious adverse events on AADvac-1 treatment during the trial. Three serious events were deemed unrelated to treatment and included troponin-T elevation, breast cancer (female), and syncope by the treating physician. Two serious adverse events (viral infection and epileptic seizure) that occurred in the same patient in short succession were judged to be possibly related to treatment; however, an independent data and safety monitoring board assessed the possibility of an association between these events and AADvac-1 as unlikely. Two patients withdrew from the trial, one because of serious adverse events and the other because of raised troponin-T and personal reasons, but the most common adverse event was injection site reaction after administration (occurring in 53% of patients). While no cases of meningoencephalitis or vasogenic edema occurred after administration, one patient with pre-existing microhemorrhages had newly occurring microhemorrhages, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores, considered to be the "gold standard" for assessing anti-dementia treatments on neuropsychological function, remained stable in all subjects. Overall, it was determined that AADvac-1 had a favorable safety profile and excellent immunogenicity, which justified continuance to a Phase 2 trial (ClinicalTrials.gov, 2015a).

Results from the Phase 2 trial were recently presented at the 2020 Advances in Alzheimer's and Parkinson's Therapies Focus Meeting (AAT-AD/PD) (Alzforum.org, 2020). This trial

used patients with mild AD by NIA-AA criteria that had a magnetic resonance imaging (MRI) consistent with diagnosis, or in a few cases, cerebrospinal fluid A β and tau levels consistent with AD. Patients received subcutaneous injections of 40 μ g AADvac1 or placebo once a month for six months, followed by quarterly booster doses thereafter. Altogether, a total of eleven doses of vaccine were administered and participants were followed for two years. The primary outcome was safety, which was met. The vaccine was well-tolerated, and other than injection-site reactions there was no difference in adverse events between vaccine and placebo groups. Secondary outcomes included a custom cognitive battery, the Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SB) scale, the Alzheimer's Disease Cooperative Study – Activities of Daily Living questionnaire (ADCS-ADL) as well as measures of immunogenicity. It was reported that throughout the trial participants maintained about 1.5 μ g/ml antibodies, which was deemed a robust immune response to the vaccine. Further, of the antibodies produced by the vaccine-treated group, most had an affinity for tau of 1 nM or better, which is similar to that of tau monoclonal antibodies. For exploratory outcomes, the significant difference between groups in plasma neurofilament light chain (NfL) indicated a protective effect of AADvac1 on neurodegeneration. This effect was seen mostly during the second year of treatment, when NfL levels stabilized in the vaccinated participants. While no overall cognitive benefit over placebo was detected, a preplanned subgroup analysis of participants 67 years or younger indicated a slowing of cognitive decline by 42 percent on the CDR-SB, 31 percent on the MMSE, and 26 percent on the ADCS-ADL in the treatment group; however, this was not statistically significant. This same subgroup did show more robust biomarker changes than the full cohort, namely in plasma NfL and cortical atrophy on MRI, which was statistically significant. CSF biochemistry was assessed in some but not all participants, and while p-tau181 and p-tau217 dropped in the treatment group, no significant changes were reported. As a result of these outcomes, particularly in younger AD patients, Axon Neuroscience is planning a Phase 3 trial that will run for 24–30 months.

A separate open-label Phase 1 pilot trial was initiated in June of 2017 in patients with non-fluent/agrammatic variant progressive aphasia (PPA). This trial will use two doses of AADvac-1 over a series of six weekly subcutaneous injections, followed by five booster shots spaced 13 weeks apart. The primary outcomes include adverse events and measures of immunogenicity, while secondary outcomes include change in CSF and serum biomarkers (neurogranin, phosphorylated neurofilament heavy chain protein, ubiquitin, tau, phospho-tau pT181, N-terminal tau, amyloid- β 1–40, amyloid- β 1–42, ubiquitin, α -, β -, and γ -synuclein, YKL-40, MCP-1 and neurofilament light chain protein, respectively), MRI, temporal change in immune cell populations (granulocyte, monocyte, and lymphocyte), correlations of immunological predictors with IgG antibody titers, and a range of clinical measures including Frontotemporal Lobar Degeneration Clinical Dementia Rating Sum of Boxes (FTLD-CDR-SB), Clinician's Global Impression – Improvement (CGI-I), Instrumental Activities of Daily Living (ADL), a Custom Cognitive Battery, Addenbrooke's Cognitive Examination, Unified Parkinson's disease rating scale (UPDRS) part III, and Frontal Systems Behavior Scale (FrSBe) (ClinicalTrials.gov, 2017a).

ACI-35:

ACI-35 is a liposome-based vaccine that aims to elicit an immune response to pathological conformers of phosphorylated tau without also mounting autoimmune B cell or T cell responses against physiological forms of tau (Hickman et al., 2011). The vaccine contains 16 copies of a synthetic tau fragment that is phosphorylated at residues serine-396 and serine-404 of the tau protein that is anchored to a lipid bilayer and administered with the adjuvant MPLA.

Pre-clinically, a three-month regimen of subcutaneous ACI-35 injections elicited, rapidly and robustly, specific antisera against phospho-serine-396, 404 tau in both wild-type and P301L mutant tau transgenic mice (Theunis et al., 2013). The resulting antibodies bound neurofibrillary tangles in mouse brain tissue sections and reduced soluble and insoluble tau in brain extracts. Translationally, ACI-35 also aided in the retention of body weight, delayed the onset of clasping, and extended the lifespan of the mice, but did not improve endurance on a rotarod test. No evidence of gliosis, T cell activation, or any other inflammatory markers were detected.

In December of 2013, AC Immune began a Phase 1b study comparing six-month courses of low, medium, and high doses of ACI-35 in patients with mild to moderate AD (Alzforum.org, 2018a; ISRCTN, 2016). Initial dosing was followed by a subsequent booster shot and a six-month safety observation period. Primary outcomes were safety, tolerability, and immunogenicity, which included MRI and electrocardiogram (ECG) measurements, biochemistry measures from CSF, and antibody titers from blood. Secondary outcomes were biomarkers and clinical/functional outcomes including ADAS-Cog, Mini-Mental State Examination (MMSE), trail-making and fluency tests, Clinical Global Impression of Change Disability Assessment in Dementia, and Neuropsychiatric Inventory Scale. The results of this trial were also recently reported at the 2020 AAT-AD/PD meeting (Alzforum.org, 2020). The vaccine was well-tolerated but had to be redesigned following a weak immune response. A second adjuvant plus an epitope that activated the HLA-DR receptor on T-cells were also added as part of the new design. This second-generation vaccine, ACI-35.030, produced a stronger immune response in rhesus monkeys. Vaccination with ACI-35.030 generated 50 times as many antibodies compared to ACI-35 and booster shots bolstered this effect. Antibodies generated by the new vaccine were specific for p-tau over tau, similar to ACI-35, and showed about 100-fold sensitivity in rhesus monkeys. These antibodies also recognized paired helical filaments from AD brain as well. In 2015 ACI-35 was license to Janssen. A multicenter Phase 1b/2a safety and immunogenicity study in AD patients is planned as a collaboration between Janssen and AC Immune, but details of this trial are not currently listed in any trial registries.

BIIB092:

In review, Bristol-Myers Squibb acquired iPerian, a biotechnology company that had developed IPN007, a mouse monoclonal antibody against extracellular, N-terminally fragmented forms of tau (eTau) that were originally isolated from familial AD patient-derived pluripotent stem cells. The rationale for this therapeutic approach is that eTau is proposed to be involved in the spread of pathology in tauopathies. In the original

publication, it was demonstrated that neutralizing eTau reduced A β in primary human cortical neurons whereas exogenously adding eTau increased A β levels (Bright et al., 2015). Further, it was shown that neutralizing eTau in two different human tau transgenic mouse models also reduced A β levels. Lastly, the authors proposed neuronal hyperactivity as a mechanism by which this regulation occurs and showed that hyperactivity regulated both eTau secretion and A β production. Taken together, these results suggest a dynamic mechanism of positive feed forward regulation in that eTau further increases A β levels, perpetuating a vicious cycle (Bright et al., 2015).

Bristol-Myers Squibb ran a single-center, single ascending-dose study in healthy volunteers to assess safety parameters for up to eight months after administration (Qureshi et al., 2018). Next, a multi-center, multiple ascending-dose Phase 1 trial began in patients with PSP. Participants received doses of up to 2,100 mg, infused once every four weeks for 12 weeks and were assessed for safety, pharmacology and immunogenicity (ClinicalTrials.gov, 2015b). An 18-month open-label extension study was offered to participants and is still running (ClinicalTrials.gov, 2016a).

Biogen ultimately licensed the humanized IgG4 antibody and in June of 2019 the results from the Phase 1B trial in patients with progressive supranuclear palsy (PSP) were published, revealing details on safety, tolerability, pharmacokinetics, and pharmacodynamics (Boxer et al., 2019). Briefly, repeated administration of BIIB092, at doses of up to 2100 mg, was deemed safe and well-tolerated in PSP patients. No deaths, serious treatment-related adverse events, or discontinuations due to an adverse event were reported. Most adverse events were mild or moderate, with no treatment-related or dose-related trends in frequency or severity. Concentration of BIIB092 in CSF was increased with higher doses, and the effective half-life was estimated to be about 28 days, based on the two-fold accumulation seen on day 57 compared with day 1, which is consistent with the half-life seen in healthy volunteers.

In PSP patients, all BIIB092 doses suppressed cerebrospinal fluid (CSF) un-bound N-terminal tau concentrations by more than 90 percent, indicating target engagement, whereas unbound N-terminal tau concentrations remained unchanged in the placebo group. While no dose response was observed, a post hoc analysis comparing N-terminal tau to plasma drug exposure teased out a modest correlation, with the lowest exposure reducing N-terminal tau by 91 percent and the highest by 96 percent. No change in exploratory clinical endpoints and bio-markers, including MRI scans and CSF levels of total tau, ptau181, A β 42, or neurofilament light chain were detected; however, this was expected given that treatment lasted only three months. The participants in the Phase 1b study are currently enrolled in an ongoing extension study. The results of this study confirmed the findings of the Phase 1 study and informed the design of the subsequent Phase 2 study, which had a longer treatment period and enrolled a larger group of participants with PSP (ClinicalTrials.gov, 2017c). Unfortunately, in December 2019 Biogen announced that BIIB092 had failed in the Phase 2 trial for people with PSP (Alzforum.org, 2019b; Investors.biogen.com, 2019). This was not particularly surprising as discussed previously (Colin et al., 2020; Sigurdsson, 2017, 2018). The original mouse antibody was reported not to enter cells (Bright et al., 2015). Assuming that the humanized version retained this property and considering that CSF tau

levels are not altered in PSP compared to control subjects, it was unlikely to work in this patient population. However, the Phase 2 study for patients with mild cognitive impairment (MCI) due to suspected Alzheimer's disease (AD) or with early AD is continuing. The primary objective of this trial is to evaluate the long-term safety and tolerability of BIIB092 in participants with MCI due to suspected AD or with mild AD. The secondary objectives are to evaluate the efficacy of multiple doses of BIIB092 in slowing cognitive and functional impairment, and to evaluate the immunogenicity of BIIB092 after multiple doses in participants with AD-related MCI or with mild AD (ClinicalTrials.gov, 2017b).

Lastly, it was announced that the Phase 1 for four different primary tauopathy syndromes: amyloid- β PET negative corticobasal syndrome (CBS), nonfluent variant primary progressive aphasia (nfvPPA), symptomatic patients with autosomal dominant genetic forms of frontotemporal lobar degeneration (FTD) due to the presence of a mutation in the microtubule-associated protein tau gene (MAPT), and traumatic encephalopathy syndromes (TES) would be terminated based on differences in disease pathology, according to the company's press release (ClinicalTrials.gov, 2019a; Investors.biogen.com, 2019).

While the failure of this antibody in patients with PSP was disappointing, targeting extracellular tau may be more advantageous in the ongoing trials with MCI and early AD patients, where CSF tau is increased relative to controls. That being said, targeting the small pool of N-terminus fragments may not be sufficient to halt or reverse the progression of the disease, as the levels are extremely low in CSF, compared to intracellular tau levels.

BIIB076:

BIIB076 is a human recombinant, monoclonal anti-tau antibody that was originally generated by Neurimmune's reverse translational medicine platform and was later acquired by Biogen in 2010. While no cell-based or mouse preclinical work with this antibody has been published, Biogen has publicly reported that BIIB076 binds with subnanomolar affinity to human and cynomolgus monkey recombinant tau, and recognizes monomeric and fibrillar forms of tau as well as tau isolated from healthy human and Alzheimer's disease brains (Alzforum.org, 2018b). It was further reported that in young monkeys, a single dose (100 mg/kg) of BIIB076 had a half-life in blood of eight to eleven days and reached maximum CSF concentration in 24–48 h but that its CSF concentration was 1,000 times lower than in plasma. Biogen also reported that total tau concentration in plasma rose while CSF total tau stayed unchanged but free CSF tau unbound to BIIB076 dropped 75% 24-h after administration and returned to baseline after three-weeks. Together, Biogen indicated this was evidence of target engagement.

A separate toxicity study evaluated three doses of up to 16 times the highest predicted efficacious dose, compared to vehicle, given intravenously or subcutaneously over the course of a month to young cynomolgus monkeys (Czerkiewicz et al., 2017). Dose-dependent increases in serum BIIB076 levels and CSF total and free tau was reduced at the highest doses used.

In February 2017 Biogen started recruiting for an ascending-dose Phase 1 trial in healthy volunteers and mild AD, as determined by CSF A β 42, total tau, and phosphorylated tau

levels (ClinicalTrials.gov, 2019c). Participants are being given a single intravenous infusion and healthy volunteers are grouped into five successive dosing cohorts while AD patients are grouped into two. Primary outcomes include adverse events, clinical labs, vital signs, neurological exam, electrocardiogram (ECG), and MRI; secondary outcomes include eight pharmacokinetic parameters of exposure and clearance, as well as BIIB076 immunogenicity.

With the limited information regarding the characteristics of this antibody, it is difficult to speculate how efficacious it may be in a diseased population. As outlined in the ‘Characteristics of the Tau Antibody – Isotype, epitope, charge, affinity, and size’ section, these parameters will impact performance greatly. Based on preclinical findings, if this antibody is readily taken up into neurons and binds tau aggregates, it stands a chance to significantly reduce disease progression and/or improve cognitive performance in an AD population in a subsequent Phase 2 trial.

CN2-8E12 (ABBV-8E12):

8E12 is a humanized IgG4 antibody being developed by C2N Diagnostics and AbbVie to treat tauopathies. This antibody recognizes an N-terminal sequence of tau. The original mouse antibody was reported not to be taken up into neurons and thereby thought to only work extracellularly (Yanamandra et al., 2013). Similarly to BIIB092, its uptake into neurons is not required for efficacy in preclinical models. The mouse version of this antibody blocked seeding in a cell-based tau sensor assay (Kfoury et al., 2012). In P301S tau-transgenic mice, it reduced brain neurofibrillary pathology, insoluble tau, microgliosis, seeding activity by the lysate of treated brain, brain atrophy, and deficits in the conditioned fear response (Yanamandra et al., 2015; Yanamandra et al., 2013).

AbbVie and C2N initially conducted a single-ascending-dose study, comparing four doses of 8E12 (2.5 mg/kg to placebo) in participants with PSP in successive, three-to-one randomization groups and followed these participants 84 days after dosing (ClinicalTrials.gov, 2018b). The goals were to find the maximum tolerated dose, and outcomes included safety, tolerability, immunogenicity, and pharmacokinetics. Results were publicly presented, and showed 8E12 as being safe, but that a maximum tolerated dose was yet to be determined in this trial. The half-life of the antibody was determined to be 27–37 days, with dose-related exposure in blood and a CSF-to-blood ratio of 0.18–0.35. From here, an open-label extension study started to assess 8E12’s longer-term safety and tolerability in participants in this trial who might otherwise be ineligible for the subsequent Phase 2 trial.

In October 2016, a Phase 2 trial in people who meet diagnostic criteria for AD, as defined by a CDR rating of 0.5, an MMSE of 22 or higher, and a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score of 85 or lower, was initiated by AbbVie (ClinicalTrials.gov, 2016e). These parameters were used to define ‘early disease stage’, and this trial is comparing three doses of 8E12 to placebo that are infused over a period of 96 weeks and include a 16-week follow-up. The primary outcomes are decline on the CDR-SB and adverse events. Besides blood-based pharmacokinetic parameters for the 8E12 antibody, secondary outcomes include a range of clinical and functional measures such as the Alzheimer’s Disease Assessment Scale Cognitive Subscale 14 (ADAS-Cog14), RBANS, Functional Activities Questionnaire (FAQ), and Alzheimer’s Disease Cooperative Study/

Activities of Daily living scale adapted for MCI patients (ADCS-MCI-ADL-24). No tau-based target engagement outcomes are listed. An extension study to assess 8E12's longer-term safety and tolerability in participants in this trial is also underway (ClinicalTrials.gov, 2018a).

In December 2016, a separate Phase 2 trial who are 40 or older and have had PSP symptoms for fewer than five years was initiated by AbbVie (ClinicalTrials.gov, 2016d). Primary outcomes are decline on the PSP Rating Scale (PSPRS) Total Score and adverse events; secondary outcomes include pharmacokinetic, MRI, as well as global and Parkinson's clinical measures. A 4-year extension study to this trial in people who have completed the placebo-controlled treatment phase began in January 2018. All participants are randomized to 8E12, and the trial stays randomized to dose. Primary outcomes are decline on the PSPRS Total Score for up to 5 years; secondary outcomes include change on Parkinson's and global clinical measures (ClinicalTrials.gov, 2018c).

Unfortunately, in late July 2019 it was announced that AbbVie had called a halt to the Phase 2 trial of 8E12 in patients with PSP due to a failed futility analysis ([Alzforum.org](https://www.alzforum.org), 2019a). At this time, it was also announced that this would end two extension studies evaluating 8E12 in patients with PSP and the pre-approval access program (PAA) to this antibody for primary tauopathies. The Phase 2 trial in patients with mild cognitive impairment (MCI) and early dementia due to AD will continue without changes.

Assuming that the humanized antibody only worked extracellularly as proposed for the original mouse antibody, that feature may explain why the antibody failed. As well documented and discussed previously (Colin et al., 2020; Congdon and Sigurdsson, 2018; Sigurdsson, 2017, 2018), CSF tau levels are not increased in PSP patients. Hence, extracellular tau is unlikely to have a role in tau pathogenesis in PSP. Targeting it in that patient population may, therefore, be futile. However, much like BIIB092, the outcome of the trial using an AD population will inform us as to whether targeting extracellular N-terminus fragments is worthwhile.

LY3303560:

LY3303560 is a humanized anti-tau antibody that binds to a discontinuous conformational epitope of tau. This antibody was likely derived from the conformational antibody MC1 (Jicha et al., 1997), which has been shown to be effective in different in vivo or ex vivo mouse studies (Chai et al., 2011; d'Abramo et al., 2013; Luo et al., 2015; Schroeder et al., 2016). Preclinically, an intravenous administration of LY3303560 to monkeys indicated clearance of 0.15 ml/ h/kg and a half-life of 13 days, while subcutaneous administration indicated a bioavailability of 79 percent (Alam et al., 2017). Rat CSF concentration was 0.1 percent of plasma at 24 h after intravenous administration.

In April 2016 Eli Lilly & Co. initiated a Phase 1 trial in both healthy volunteers and patients with AD-related MCI or mild to moderate AD, as ascertained with a positive amyloid- β PET scan (ClinicalTrials.gov, 2016b). The study evaluated a single, escalating intravenous infusion or subcutaneous injection and measured adverse effects up to 85 days after this dose, as well as maximum drug concentration in both serum and CSF.

In January 2017, a second Phase 1 study was initiated in an identical cohort of patients. However, this trial used an escalating-multiple-dose design and delivered LY3303560 intravenously. The trial was scheduled to last six months with four additional months of follow up. Primary outcomes include adverse events and pharmacokinetic parameters (ClinicalTrials.gov, 2017d).

In April 2018, a Phase 2 first efficacy trial began in patients with early symptomatic AD, defined by gradual and progressive decline in memory for at least six months (ClinicalTrials.gov, 2018e). This trial is comparing two intravenous doses of LY3303560. However, specific information regarding doses and treatment regimen/duration have not been made public. Primary outcomes include change from baseline on Lilly's integrated Alzheimer's Disease Rating Scale (iADRS), while secondary measures include the Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog13), the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL), CDR-SB, MMSE, the CogState Brief Battery (CBB), as well as tau PET, volumetric MRI, the Columbia Suicide Severity Rating Scale (C-SSRS), and antigenicity of LY3303560.

In preclinical mouse models, while shown to be effective at reducing tau pathology, this antibody was not taken up by neurons, suggesting that it exerted its effects by binding to and clearing extracellular conformational pathological tau (d'Abramo et al., 2013). We have seen that antibodies exclusively targeting the small pool of extracellular tau, albeit different epitopes (BIIB092, CN2–8E12 (ABBV-8E12)), have not been efficacious in PSP. Therefore, if LY3303560 does act exclusively in the extracellular compartment, and targets a potentially even smaller pool of conformational extracellular tau, it may not be sufficient to attenuate disease progression, even in AD.

RO7105705:

RO7105705 is another IgG4 antibody that was developed by AC Immune and Genentech, and targets extracellular tau. The rationale is that antibodies with a reduced effector function like IgG4 should limit microglial activation which might otherwise lead to inflammatory responses (Lee et al., 2016; Sigurdsson et al., 2016). However, this would appear to reduce their efficacy because microglial phagocytosis of tau would not be recruited. Genentech has announced that RO7105705 binds the N-terminus of all six isoforms of human tau, both monomeric and oligomeric, independent of phosphorylation, and that pre-clinically 13-weeks of treatment dose-dependently reduced brain tau pathology and increased plasma tau levels in P301L tau transgenic mice and was also deemed safe in mice and cynomolgus monkeys ([Alzforum.org](https://www.alzforum.org), 2019c).

Based on these pre-clinical findings, Genentech ran a single dose, dose-escalation, and multiple dose Phase 1 trial in healthy controls and patients with mild to moderate AD. The primary outcomes were adverse events, dose limiting adverse events, and change from baseline in suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) Score. Secondary outcomes included Change From Baseline in Global Function as Assessed Using the Clinical Dementia Rating (CDR) Global Score, Change From Baseline in Cognitive Function as Assessed Using the MMSE, serum concentrations of

RO7105705, and percentage of participants with anti-therapeutic antibodies (ClinicalTrials.gov, 2016c). Genentech has since publicly reported that single doses in healthy volunteers went as high as 16,800 mg, with a 15-day window observed between a given dose and the next higher dose, and that 70 percent of the subcutaneous doses were bioavailable. While results remained blinded at the time of announcement, the trial had not generated serious adverse events, the plasma half-life of RO7105705 was 32 days, and the plasma and CSF concentration increased with dose (Alzforum.org, 2019c).

While results of the Phase 1 trial have been presented (Kerchner et al., 2017), but not published, two separate Phase 2 trials have already been initiated. The first enrolls patients with prodromal or probable AD, determined by a positive amyloid- β PET or CSF A β 42 levels, and mild symptoms (ClinicalTrials.gov, 2017e). Patients receive one of three doses over an 18-month course, with a 96-week open label extension available for those who complete the blinded portion of the trial. Primary outcomes are change on the CDR-SB and safety, while secondary measures include the change from baseline in the RBANS, the Alzheimer's Disease Assessment Scale (ADAS), the Amsterdam Instrumental Activity of Daily Living questionnaire, the ADCS-ADL Inventory, as well as serum drug concentration and anti-drug antibodies. This trial is also using Genentech's tau PET tracer GTP1 and measures change from baseline in response to treatment. The second Phase 2 trial includes patients with probable AD, as confirmed by positive amyloid- β PET or CSF A β 42 levels, and moderate dementia (ClinicalTrials.gov, 2019d). The study comprises a screening, double-blind treatment, optional open-label extension period, and a safety follow-up period. Primary outcomes are change from baseline on both ADAS and ADCS-ADL, while secondary outcomes include change from baseline on the CDR-SB and MMSE, adverse events, serum concentration and anti-drug antibodies to RO7105705.

As with BIIB092, CN2-8E12 (ABBV-8E12), and possibly LY3303560, targeting extracellular tau is less likely to be efficacious than targeting both extra- and intracellular tau; however, the ongoing trials on AD patients is the best way to test this hypothesis.

RG7345:

RG7345 is a humanized monoclonal antibody targeting tau phosphorylated at serine 422, and was originally derived from a rabbit monoclonal antibody (Congdon and Sigurdsson, 2018). Pre-clinically, RG7345 was shown to enter neurons and lysosomes and reduce tau pathology in TauPS2APP triple transgenic mice (Collin et al., 2014).

In 2015 Hoffman-La Roche initiated a single-ascending-dose Phase 1 trial using healthy male patients to assess safety, tolerability, and pharmacokinetics following an intravenous infusion. However, the results of this trial have never been made public and the antibody has since been discontinued by Roche. It is presumed that the antibody had an unfavorable pharmacokinetic profile, because no safety or efficacy concerns have ever been raised (Congdon and Sigurdsson, 2018).

JNJ-63733657:

JNJ-63733657 is a monoclonal antibody that recognizes the mid-domain of tau; however, the exact epitope has yet to be disclosed. The rationale for targeting the mid-domain of tau is

that antibodies targeting this region are more likely to interfere with cell-to-cell propagation of tau, based on its abundance in CSF, as mentioned above in Type of Tauopathy Being Targeted.

In 2017, Janssen initiated a two-part Phase 1 trial to assess the primary outcomes of safety and tolerability of JNJ-63733657 following single ascending intravenous dose administration in healthy subjects (Part 1) and multiple ascending intravenous dose administrations in subjects with prodromal or mild AD (Part 2), as defined by a CDR Scale global rating of 0.5 or 1.0 at the time of screening and CSF consistent with AD pathology (ClinicalTrials.gov, 2017f). Secondary outcomes included pharmacokinetic parameters and immunogenicity of JNJ-63733657 in serum and CSF.

A separate Phase 1 trial was initiated in 2018 to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of JNJ-63733657 following a single ascending intravenous dose in healthy Japanese participants as well (ClinicalTrials.gov, 2018d).

Based on the target epitope, this antibody is likely to be more efficacious extracellularly than the N-terminally targeting antibodies due to its relative abundance in CSF. Furthermore, if the antibody is taken up into neurons to access the larger pool of intracellular tau, its potential to be disease-modifying would be substantially improved.

UCB0107:

UCB0107 is a monoclonal antibody that also binds the mid-domain of tau, specifically amino acids 235–250 near tau's microtubule-binding domain. As with JNJ-63733657, the rationale is that a mid-domain targeting antibody is likely to be more efficacious than an N-terminally targeting antibody based on its ability to interfere with transneuronal propagation of pathogenic, aggregated tau. Compared to various reference antibodies, including the original mouse versions of some of the clinical antibodies mentioned above, it showed greater efficacy than the others in a cell-based assay (Courade et al., 2018). In vivo, the mouse version of UCB0107 prevented the induction of tau pathology in the brains of transgenic mice that had been injected with human AD-derived brain extracts, showing that it could effectively neutralize the pathological species present in these extracts (Albert et al., 2019). It was also capable of blocking the progression of tau pathology to distal brain regions compared to a N-terminal targeting antibody, which was less effective at blocking tau seeding in vitro, and showed less efficacy in reducing AD homogenate driven tau pathology in the transgenic mouse model.

In 2018, UCB Biopharma initiated two independent Phase 1 trials. The first is assessing the safety and tolerability of single ascending doses of UCB0107 in healthy participants. Primary outcomes include incidence of adverse events, while secondary outcomes include UCB0107 exposure in blood and CSF, pharmacokinetic parameters of antibody distribution and clearance, as well as presence of anti-UCB0107 host antibodies (ClinicalTrials.gov, 2018g). The second is examining safety, tolerability, and serum pharmacokinetics following a single dose of UCB0107 in healthy participants (ClinicalTrials.gov, 2018f).

While ongoing trials are only using healthy participants, similarly to JNJ-63733657, targeting the mid-domain of tau in AD or PSP populations in future Phase 2 trials has therapeutic potential. Further, if this antibody is also capable of targeting this epitope intracellularly, it has an even greater chance of being disease-modifying.

Lu AF87908:

Lu AF 87908 is currently in a Phase 1 safety and tolerability testing in healthy individuals and patients with AD (ClinicalTrials.gov, 2019e). It binds to the phospho-serine 396 region and the original mouse antibody has shown efficacy in preclinical models (Rosenqvist et al., 2018). Specifically, it reduced tau seeding in cellular and mouse models of tauopathy. Furthermore, AD brain extracts depleted with the antibody could not seed tau in vitro or in vivo, indicating that it neutralizes seed-competent pathological tau protein.

PNT001:

In October 2019, Pinteon Therapeutics announced the launch of a Phase 1 trial in healthy volunteers of the company's lead asset, PNT001, which targets a highly neurotoxic conformation of tau, known as *cis*-pT231 tau. PNT001 aims to disrupt the spread of this toxic form of tau by precisely targeting and neutralizing pathologic tau containing the *cis*-pT231 epitope (Businesswire.com, 2019). *Cis*-pT231 was identified in multiple preclinical studies as a potent driver of neurodegenerative disease, where treating traumatic brain injury (TBI) mice with an IgG2b mouse monoclonal antibody against *cis*-pT231 prevented tauopathy development and spread, and restored many TBI-related structural and functional sequelae (Albayram et al., 2017; Kondo et al., 2015). The Phase 1 trial consists of five single escalating dose levels and examines safety, tolerability, and pharmacokinetics (ClinicalTrials.gov, 2019b). The company also plans to move into one or more Phase 1 trials of multiple ascending doses in patients with TBI, PSP, or AD, with tau pathology as a central component of each disease state.

8. Conclusions and future directions

While major advancements have been made, and we continue to learn from what are deemed “failures” in the field and related fields, we hope that by highlighting key considerations for further developments we facilitate the search for an effective disease-modifying therapeutic targeting pathological tau. Although it will be several years before we know the outcome of many of the current clinical trials, there are many reasons to remain optimistic about the future of tau immunotherapies.

Firstly, with the successful completion of many Phase 1 trials, safety concerns remain low. Secondly, targeting tau protein is more likely to provide therapeutic benefits later in the disease process than A β since tau pathology correlates better with the degree of dementia than A β lesions (Nelson et al., 2012). Thirdly, as the ongoing A β immunotherapy trials have taught us, it is important to continue to develop second and third generation approaches for tau immunotherapies. Smaller antibody fragments, like sdAbs and scFvs, should have better access into the brain and into neurons and allow them to bind to different tau epitopes than whole antibodies, providing added diagnostic and therapeutic benefits. Because of their

smaller size, they are also better suited for gene therapies than whole antibodies. We look forward to the current and future basic research investigating these antibody fragments as alternative therapeutic approaches. Lastly, a shift in the timing of intervention to the MCI stage or the very early stage of AD and the running of parallel trials in primary tauopathies (such as PSP) has been a feature of many recent trials. Based on some of the key considerations discussed in this review, such as presence/abundance of intracellular and extracellular pools of tau and/or epitopes present, appreciating that an antibody may possess disease-specific efficacy, and separately assessing an antibody's efficacy against tau seeding and toxicity are important steps in the right direction for future preclinical studies and clinical trials.

As discussed in the Characteristics of the Tau Antibody, Type of Tauopathy to Determine Intracellular or Extracellular Target, and Prevention of Toxicity vs Seeding sections, it was disappointing but of little surprise that two different extracellularly acting N-terminally targeting IgG4 antibodies (BIIB092 and CN2-8E12 (ABBV-8E12)) failed in PSP patients. While these two therapeutics showed great promise in preclinical and Phase 1 trials, based on the limited available information, we can assume that either the epitopes, isotype, disease population, or a combination of the three, were not a good clinical fit. With their respective characteristics in mind, these two therapeutics may be better suited for the ongoing trials in AD patients, where extracellular/ CSF tau is increased, relative to PSP. Findings from those trials will better elucidate whether reducing extracellular pools of tau is sufficient to curtail AD progression. Looking forward, we anticipate that antibodies targeting the more abundant pools of mid-domain of tau (JNJ-63733657 and UCB0107), phospho epitopes of tau (Lu AF87908, PNT001), and conformational forms of tau (LY33033560 and BIIB076), may fare better in AD populations. Certainly the continuation of basic research into the underlying causes of tau dysfunction in AD and other tauopathies is essential for identifying new targets for therapeutic intervention. We maintain our optimism for the eventual success of tau immunotherapies and look forward to the basic research findings and clinical trial outcomes ahead.

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HIGHLIGHTS

- Many clinical trials for Alzheimer's disease are tau immunotherapies.
- The development of tau immunotherapies is complex as outlined in this review.
- Barriers to success and suggestions for future clinical trials are discussed.
- An up-to-date status of current clinical trials is also provided.

Table 1

Clinical Trials of Tau Immunotherapies. List of active and passive tau immunotherapies in clinical trials. If available, information is provided on the epitope of the immunogen/antibody and the subject groups included.

Name	Synonyms	Therapy Type	Tau Epitope	Subjects (Trial Status)	Company
AA Dvac-1	Axon peptide 108 conjugated to KLH	Active	294–305	Alzheimer's Disease (Phase 2), Progressive Nonfluent Aphasia (Phase 1)	Axon Neuroscience SE
ACI-35		Active	P-Ser396,404	Alzheimer's Disease (Phase 1)	AC Immune SA - Janssen
BIIB092	Gosuranemab, BMS986168, IPN007	Passive	8–19	amyloid PET (–) corticobasal syndrome, nonfluent variant primary progressive aphasia, symptomatic patients with autosomal dominant genetic forms of frontotemporal lobar degeneration due to the presence of a mutation in the microtubule-associated protein tau gene, and traumatic encephalopathy syndromes (Phase 1 - Discontinued), Progressive Supranuclear Palsy (Phase 2 - Discontinued), Alzheimer's Disease (Phase 2)	Biogen, (Bristol-Meyers Squibb; iPerian)
BIIB076	NI-105,6C5 huIgG1/1	Passive	Undisclosed; binds monomeric and fibrillar forms of human and cynomolgus monkey recombinant tau and tau isolated from healthy human and Alzheimer's disease brains	Healthy, Alzheimer's Disease (Phase 1)	Biogen, Neurimmune
CN2-8E12	ABBV-8E12	Passive	25–30	Progressive Supranuclear Palsy (Phase 2 - Discontinued), Alzheimer's Disease (Phase 2)	AbbVie (C2N Diagnostics)
LY3303560		Passive	Conformational (7–9, 312–342)	Healthy, Alzheimer's Disease (Phase 2)	Eli Lilly
RO7105705	MTAU9937A, RG6100	Passive	N-terminus	Alzheimer's Disease (Phase 2)	AC Immune SA - Genentech - F. Hoffman La Roche AG
RG7345	RO6926496	Passive	P-Ser422	Healthy (Phase 1 - Discontinued)	F. Hoffman La Roche AG
INJ-63733657		Passive	Undisclosed; Middle region	Healthy, Alzheimer's Disease (Phase 1)	Janssen
UCB0107	UCB 0107	Passive	235–250	Healthy (Phase 1)	UCB Biopharma
Lu AF87908		Passive	P-Ser396	Healthy, Alzheimer's Disease (Phase 1)	H. Lundbeck A/S
PNT001		Passive	<i>cis</i> -pT231	Healthy (Phase 1)	Pinteon Therapeutics